IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Nirmal Mulye	**Examiner:**	Nissa M. Westerberg
Serial No.:	10/800,984	**Art Unit:**	4173
Filed:	March 15, 2004	**Docket:**	14276
For:	A PROCESS FOR PREPARING SUSTAINED RELEASE TABLETS	**Confirmation No:**	2376

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF NIRMAL MULYE
PURSUANT TO 37 C.F.R. §1.131

Sir:

I, Nirmal Mulye, hereby declare and state as follows:

1. I am an applicant of the above-identified application.

2. I have been advised that the United States Patent and Trademark Office has alleged that the present application contains four inventions and based upon our election, the United States Patent and Trademark Office ("USPTO") has restricted the subject matter herein to a sustained release pharmaceutical composition.

3. More specifically, the present invention is directed, among other things, to a sustained release pharmaceutical composition in oral dosage form comprising a pharmaceutically effective amount of a drug, a sustained release carrier in an effective amount to retard the release of the drug from said composition when placed in an aqueous system, a water insoluble or partially water insoluble cellulose, and maltodextrin, wherein the weight ratio of

cellulose to maltodextrin ranges from about 50:1 to 1:50, and optionally a lubricating effective amount of a lubricant.

4. It is also my understanding that the USPTO has cited PCT application WO 03/026637 ("PCT application") against the present invention in a recent Office Action. I have been advised by counsel that this PCT application was published on April 3, 2003, and designates for filing the USPTO the U.S. and that its international filing date is September 27, 2002.

5. I have completed the invention disclosed and claimed in the above identified application in either the USA, NAFTA country or a WTO member country prior to September 27, 2002, the international filing date of the PCT application.

6. The completion of this invention comprised the preparation of various sustained release drug pharmaceutical compositions comprised of a drug, a sustained release carrier, a water insoluble or particularly water insoluble cellulose and maltodextrin and optionally, lubricant, in the amounts recited in Paragraph 3 wherein the weight ratio of cellulose to maltodextrin ranges from about 50:1 to about 1:50.

7. As evidence thereof, annexed hereto and made a part hereof are Exhibits A-C consisting of photocopies of Product Development Records of embodiments of the present invention.

8. The acts described in the photocopies were conducted prior to September 27, 2002 by me or by scientists and/or technicians working under my direct supervision or control. Data and information not pertinent to the invention and dates have been masked out in the preparation of these photocopies.

9. Exhibit A, consisting of two pages, is a photocopy of a Product Development Record for a 500 mg uncoated sustained release formulation of clarithromycin containing 500 mg of the drug, 315.52 mg silicified microcrystalline cellulose (ProSolv 50), maltodextrin, 19.6 mg, PEG 3350, 2.5 mg glyceryl behenate (compritol 880 ATO) and 14.7 mg lubricant (magnesium stearate). The ratio of silicified microcrystalline cellulose to maltodextrin in the embodiment was about 3:1. This exhibit describes the preparation of a tablet by dry mixing the various components identified in this paragraph and then by compressing the mixture into tablets. Five tablets were prepared, and the weight, length, thickness, breadth and the hardness of each of the tablets were measured. In addition, the friability of the tablets was determined.

10. Exhibit B, consisting of two pages, is a photocopy of the dissolution study of the clarithromycin tablet described in Exhibit A. The dissolution in the study was measured by utilizing high-pressure liquid, chromatography. The clarithromycin tablet was placed in water containing Na_2HPO_4 and the pH was adjusted to 14 using H_3PO_4 and methanol. Using high pressure liquid chromatography (HPLC), the amount of dissolution of clarithromycin was measured at 1 hour, 3 hours, 5 hours and 7 hours after the tablet was placed in the aqueous solution. In the samples tested, at the end of 7 hours, about 64.7% was released in the aqueous solution.

11. Exhibit C describes the preparation of 250 mg sustained release formulation of mesalamine. The formulation contained 100 mg mesalamine, 40 mg. of silicified microcrystalline cellulose, 21 grams of maltodextrin and 30g of an aqueous ethyl cellulose dispersion (Surelease®). The tablet was prepared by mixing the drug silicified microcrystalline cellulose and maltodextrin, wet granulating the mixture with the aqueous dispersion of ethyl

cellulose, then passing the wet mass product, which was formed through an extruder to form a rod shaped particles, and then through a spheronizer and subsequently drying the granules. Good granules were obtained as a result of this procedure.

12. All of the documents described herein were generated prior to September 27, 2002. These embodiments clearly show that the elected invention as defined in Paragraph 3 hereinabove, was completed prior to September 27, 2002.

13. I further declare that all statements made herein of my own knowledge is true and that all statements, made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so make are permissible by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 7/28/08

Nirmal Mulye

EXHIBIT A

PRODUCT DEVELOPMENT RECORD

Name of the Product :- Clarithromycin. ER Tablets Product Developed For :- No Stum

Batch No. :- RAD/07/02 Date of Trial :- REDACTED

Batch size :- 100 tab. Label Claim :- 500 mg. Overages :- —

Clarithromycin.

Sr. No.	Ingredients	RM Source	Qty. Per Tablet	Qty. Per Batch
1.	Clarithromycin.	Medicorp.	500	50
2.	Prosolv 50 75	Mendell	315.52	31.55
3.	Maltodextrin M180 25	Grain Process.	105.17	10.52
4.	PEG-3350 2.0%	Dow	19.6	1.96
5.	Compritol 888 ATO (5%)	Gattefosse	25	2.50
6.	Mg. Stearate 1.5%	Cova	14.7	1.47
		Tablet wt.	980	

(Prosolv : Malto (75:25) combination is used to get slightly slower release than the batch with 100% prosolv 50)

MANUFACTURING PROCEDURE

Procedure :- 1. Pass 1-6 thro' #40 & mix well for 10 min

2. compress.

A) Dry Mixing :-

Moisture content (%) :-

Equipment Used :- Bag mixing

Mixing Time :- Started at :- 2.30 pm Stopped at :- 2.40 pm

B) Lubrication :-

Mixing time with lubricant :- 2.30 pm Stopped at :- 2.40 pm.

Started at :-

Done by :-

Evaluation of powder blend :

Flow of powder blend was good.

Compression :

Temp : 22°c Humidity : 40% RH

Punches :

1. Description : 20x10 mm capsule shaped.
2. Upper punch : plain
3. Lower Punch : plain

No. of sets used for punching : one Hopper used : Yes/~~No~~

General Observation :

No wt. variation
No sticking observed.

INPROCESS CHECK RECORD

No.	Weight (gm)	Length (mm)	Breadth (mm)	Thickness (mm)	Diameter (mm)	Hardness (Kp)
1	0.995	20.03	10.10	5.72		13.6
2	0.980	20.09	10.11	5.72		13.0
3	0.983	20.07	10.11	5.68		13.4
4	0.981	20.09	10.12	5.69		12.0
5	1.000	20.08	10.09	5.75		14.0
6						
7						
8						
9						
10						
Avg Wt.						
RSD						
Range						13-15

Pharmacopoeial limits for tablet weight :
1) Upto 80 mg : ± 10% 2) 80 mg to 250 mg : ± 7.5% 3) Above 250 : ± 5%

Friability Test :

Initial wt of ~~10~~ 5 Tablets : 4.9549 g Wt of 10 tablets after friability test : 4.9288 g

% Friability : 0.5267

Disintegration Time : N.A.

EXHIBIT B

Clarithromycin 500 mg tab. (Uncoated)

REDACTED

Date :
Batch No.: RD107102

Dissolution study :- Analysis By HPLC

Medium : 500 ml acetate buffer pH 5.0
Speed : 50 rpm
Aliquot : 5 ml

Dissolution Machine No. : 2
Apparatus : Paddle
Dilution : 1 ml Spl + 1 ml mp

Wt. of Tablets :

1) 0.983	3) 0.980	5) 0.985
2) 0.986	4) 0.987	6) 0.980

Chromatographic system : I
Method : clarithromycin.met
Column : Phenomenex C8, Luna 10µ, 250×4.6 mm
Detection wavelength : 210 nm
Flow rate : 1 ml/min
Mobile phase :
1.911 gm NaH_2PO_4 ⟶ 245 ml water. Adjust pH to 4.0 ε diluted H_3PO_4 + 455 ml Methanol.

Standard solution :
51.2 mg clarithromycin —Sonicate for 20 min→ 25 ml Buffer
↓
(mp) 10 ml ← 1 ml

Std.:

No.	Area	RT	Area	RT
1	2188238	8.2		
2	2305513	8.2		
3				
Avg	2246875			

Sample : 1h.

Tablet	RT	Area	% Rel	Area	% Rel
1	8.4	762735	13.90		
2	8.4	745156	13.58		
3	8.5	765322	13.94	13.88	
4	8.5	730783	13.31		
5	8.5	804483	14.65		
6	8.5	762765	13.89		

CF1 = 0.347

3h

Tablet	RT	Area	% Rel	Area	% Rel
1	8·3	1795463	32·73		
2	8·3	1818836	33·15		
3	8·4	2007722	36·60	34·78	
4	8·4	1875281	34·18		
5	8·4	2045997	37·29		
6	8·4	1904724	34·72		

$cf_2 = \frac{}{0.869}$

5h

Tablet	RT	Area	% Rel	Area	% Rel
1					
2					
3			47·62		
4	8·3	2599366	~~47·38~~ 52	49·28	
5	8·3	2769423	50·74		
6	8·3	2701237	49·49		

$cf_3 = \frac{}{1.225}$

8·3 - 2100104

7h.

Tablet	RT	Area	% Rel	Area	% Rel
1					
2					
3					
4	8·2	3351603	61·58		
5	8·28	3578688	65·75	64·70	
6	8·2	3634879	66·78		

Tablet	RT	Area	% Rel	Area	% Rel
1					
2					
3					
4					
5					
6					

Inference: % Release is nearly matching with the marketed release.

EXHIBIT C

PRODUCT DEVELOPMENT RECORD

Name of the Product :– Mesalamine granules Product Developed For : – Nashm

Batch No. :– R&D/23 Date of Trial :– REDACTED

Batch size :– 100g Label Claim :– 250mg Overages :– —

Sr. No.	Ingredients	RM Source	Qty. Per Tablet	Qty. Per Batch
1	Mesalamine USP	Evoqueve	100	50
2	Prosolv 50 .70	Penwest	49	24.5
3	surelease	colorcon	30	15
4	Maltodextrin 30	Grain processing	21	10.5
		Tablet wt.	200	100

Trials at C.U.Shah college of pharmacy

MANUFACTURING PROCEDURE

Procedure :–

(1) Bag mix ingredients 1, 2, 4 for 15 mins
(2) wet granulate the above blend with surelease till wet mass forms
(3) Pass the wet mass through extruder to get rod shaped particle
(4) The above granules are passed through spheronizer at 800 rpm for 3 mins.
(5) Dry granules at 60°C for 90 mins.

A) Dry Mixing :

Moisture content (%) :
Equipment Used :

Mixing Time : Started at : Stopped at :

B) Wet Granulation :- with sustained release dispersion

Prepartion of Binding solution :-

Quantity of Binding solution used :- 60g.

(1) Wet mass passed through ~~sieve no.~~ extruder :-

Oven No. :- No. of racks used :- Drying Temp. :-

Drying started :- AM/PM Drying stopped :- AM/PM

Moisture content (%) :-

a) By KF :

Water Factor (W.F) = $\frac{15.66 \times W}{A \times 100}$

where W = wt. of sodium tartarate dihydrate in mg =

A = Titre value =

% of water = $\frac{W.F \times \text{titre value} \times 100}{\text{wt. of sample in mg}}$

(3) Moisture content % = 0.42 % of granules after using at 70°C for 2hrs.

b) By LOD :

wt. of weighing bottle + spl :-

wt. of weighing bottle :-

wt. of weighing bottle + spl :-

(After drying)

wt. of spl :-

% LOD := $\frac{\text{LOD}}{\text{wt. of sample}} \times 100$

(2) Dried granules passed through ~~sieve no.~~ spheronizer at 1800 rpm for 3 mins :-

Total wt. of granules :-

Gross :- Tare :- Net :-

Lubrication :-

Mixing time with lubricant :-

Started at :- Stopped at :-

Done by :- Nerkant.

observation :- Good granules obtained.